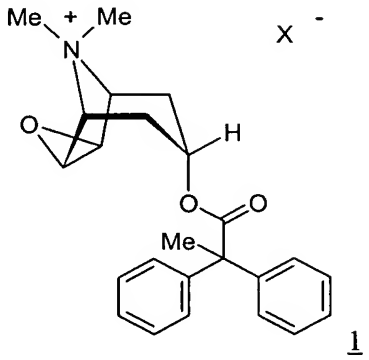
Patent Claims

1) A Pharmaceutical compositions, characterised in that they contain one or more anticholinergics of formula 1



1

wherein

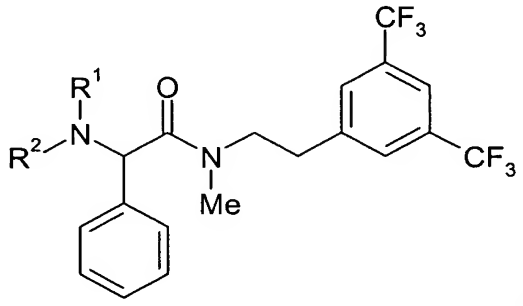
X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

combined with one or more NK_1 receptor antagonists (2), optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient.

2) The Pharmaceutical composition according to claim1, characterised in that in the compounds of formula 1 X^- is a negatively charged anion selected from the group consisting of chloride, bromide, 4-toluenesulphonate and methanesulphonate.

3) The Pharmaceutical composition according to claim 1, characterised in that in the compounds of formula 1 X^- denotes bromide.

4) The Pharmaceutical composition according to claim 1, characterised in that 2 is selected from among BIIF 1149, CP-122721, FK-888, NKP 608C, NKP 608A, CGP 60829, SR 48968(Saredutant), SR 140333 (Nolpitantium besilate/chloride), LY 303 870 (Lanepitant), MEN-11420 (Nepadutant), SB 223412, MDL-105172A, MDL-103896, MEN-11149, MEN-11467, DNK 333A, SR-144190, YM-49244, YM-44778, ZM-274773, MEN-10930, S-19752, Neuronorm, YM-35375, DA-5018, MK-869, L-754030, CJ-11974, L-758298, DNK-33A, 6b-I, CJ-11974, TAK-637, GR 205171, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-{4-[(3-hydroxy-propyl)-methyl-amino]-piperidin-1-yl}-N-methyl-2-phenyl-acetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-piperidin-1-yl]-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(cyclopropylmethyl-methyl-amino)-piperidin-1-yl]-N-methyl-2-phenyl-acetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-{4-[(2-hydroxy-ethyl)-(3-hydroxy-propyl)-amino]-piperidin-1-yl}-N-methyl-2-phenyl-acetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-{4-[cyclopropylmethyl-(3-hydroxy-propyl)-amino]-piperidin-1-yl}-N-methyl-2-phenyl-acetamide and the arylglycinamide derivatives of general formula 3



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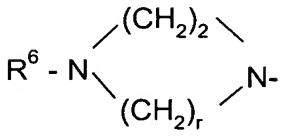
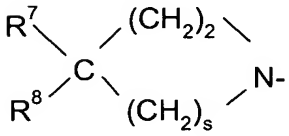
wherein

R^1 and R^2 together with the N to which they are bound form a ring of formula





wherein r and s are 2 or 3;

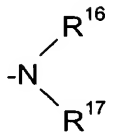
R^6 denotes H, -C_1-C_5-alkyl, C_3-C_5-alkenyl, propynyl, hydroxy(C_2-C_4)alkyl, methoxy(C_2-C_4)alkyl, di(C_1-C_3)alkylamino(C_2-C_4)alkyl, amino(C_2-C_4)alkyl, amino, di(C_1-C_3)alkylamino, monofluoro- to perfluoro(C_1-C_2)alkyl, N-methylpiperidinyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl,

R^7 has one of the meanings (a) to (d),

(a) hydroxy

(b) 4-piperidinopiperidyl,

(c)



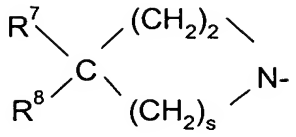
wherein R^{16} and R^{17} independently of each other denote H, (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_2-C_4)alkyl, dihydroxy(C_2-C_4)alkyl, (C_1-C_3)alkoxy(C_2-C_4)alkyl, phenyl(C_1-C_4)alkyl or di(C_1-C_3)alkylamino(C_2-C_4)alkyl,

R^8 denotes H,

optionally in the form of the enantiomers and mixtures of enantiomers thereof, optionally in the form of the racemates thereof.

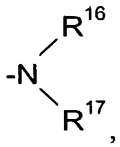
5) The Pharmaceutical composition according to claim 1, characterised in that 2 is selected from the group consisting of BIIF 1149, CP-122721, CGP 60829, MK-869, CJ-11974, GR 205171, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-{4-[(3-hydroxy-propyl)-methyl-amino]-piperidin-1-yl}-N-methyl-2-phenyl-acetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-piperidin-1-yl]-N-methyl-2-phenylacetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(cyclopropylmethyl-methyl-amino)-piperidin-1-yl]-N-methyl-2-phenyl-acetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-{4-[(2-hydroxy-ethyl)-(3-hydroxy-propyl)-amino]-piperidin-1-yl}-N-methyl-2-phenyl-acetamide, N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-{4-[cyclopropylmethyl-(3-hydroxy-propyl)-amino]-piperidin-1-yl}-N-methyl-2-phenyl-acetamide and the arylglycinamide derivatives of general formula 3, wherein

R^1 and R^2 together with the N to which they are bound form a ring of formula



wherein s is 2 or 3;

R^7 denotes a group



wherein R^{16} and R^{17} independently of each other denote H, $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_2\text{-}C_4)$alkyl, dihydroxy$(C_2\text{-}C_4)$alkyl, $(C_1\text{-}C_3)$alkoxy$(C_2\text{-}C_4)$alkyl, phenyl$(C_1\text{-}C_4)$alkyl or di$(C_1\text{-}C_3)$alkylamino$(C_2\text{-}C_4)$alkyl,

R^8 denotes H,

optionally in the form of the enantiomers and mixtures of enantiomers thereof and optionally in the form of the racemates thereof.

6) The Pharmaceutical compositions according to one of claim 1, characterised in that 2 is (S)-N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-piperidin-1-yl]-N-methyl-2-phenylacetamide or an acid addition salt thereof.

7) The Pharmaceutical composition according to claim 1, characterised in that the weight ratios of 1 to 2 are in the range from 1:100 to 100:1, preferably from 1:80 to 80:1.

8) The Pharmaceutical composition according to claim 1, characterised in that a single administration corresponds to a dosage of the combination of active substances 1 and 2 of 0.01 to 10,000µg, preferably from 0.1 to 2,000µg.

9) The Pharmaceutical composition according to claim 1, characterised in that it is in the form of a formulation suitable for inhalation.

10) The Pharmaceutical composition according to claim 9, characterised in that it is a formulation selected from among inhalable powders, propellant-containing metering aerosols and propellant-free inhalable solutions or suspensions.

11) The Pharmaceutical composition according to claim 10, characterised in that it is an inhalable powder which contains 1 and 2 in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients.

12) The Inhalable powder according to claim 11, characterised in that the excipient has a maximum average particle size of up to 250µm, preferably between 10 and 150µm.

13) A Capsule, characterised in that it contains an inhalable powder according to claim 11 or 12.

14) The Pharmaceutical composition according to claim 10, characterised in that it is an inhalable powder which contains only active substances 1 and 2 as its ingredients.

15) The Pharmaceutical composition according to claim 10, characterised in that it is a propellant-containing inhalable aerosol which contains 1 and 2 in dissolved or dispersed form.

16) The Propellant-containing inhalable aerosol according to claim 15, characterised in that it contains, as propellant gas, hydrocarbons such as n-propane, n-butane or isobutane or halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.

17) The Propellant-containing inhalable aerosol according to claim 16, characterised in that the propellant gas is TG11, TG12, TG134a, TG227 or mixtures thereof.

18) The Propellant-containing inhalable aerosol according to claim 15, characterised in that it optionally contains one or more other ingredients selected from the group consisting of cosolvents, stabilisers, surfactants, antioxidants, lubricants and means for adjusting the pH.

19) The Propellant-containing inhalable aerosol according to claim 15, characterised in that it may contain up to 5 wt.-% of active substance 1 and/or 2.

20) The Pharmaceutical composition according to claim 10, characterised in that it is a propellant-free inhalable solution or suspension which contains water, ethanol or a mixture of water and ethanol as solvent.

21) The Inhalable solution or suspension according to claim 20, characterised in that the pH is 2 - 7, preferably 2 -5.

22) The Inhalable solution or suspension according to claim 21, characterised in that the pH is adjusted by means of an acid selected from among hydrochloric acid,

hydrobromic acid, nitric acid, sulphuric acid, ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and propionic acid or mixtures thereof.

23) The Inhalable solution or suspension according to claim 20, characterised in that it optionally contains other co-solvents and/or excipients.

24) The Inhalable solution or suspension according to claim 23, characterised in that it contains as co-solvents ingredients which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters.

25) The Inhalable solution or suspension according to claim 23, characterised in that it contains as excipients surfactants, stabilisers, complexing agents, antioxidants and/or preservatives, flavourings, pharmacologically acceptable salts and/or vitamins.

26) The Inhalable solution or suspension according to claim 25, characterised in that it contains as complexing agent editic acid or a salt of editic acid, preferably sodium edetate.

27) The Inhalable solution or suspension according to claim 25, characterised in that it contains, as antioxidants, compounds selected from among ascorbic acid, vitamin A, vitamin E and tocopherols.

28) The Inhalable solution or suspension according to claim 25, characterised in that it contains as preservatives compounds selected from cetyl pyridinium chloride, benzalkonium chloride, benzoic acid and benzoates.

29) The Inhalable solution or suspension according to claim 23, characterised in that it contains, in addition to the active substances 1 and 2 and the solvent, only benzalkonium chloride and sodium edetate.

30) The Inhalable solution or suspension according to claim 23, characterised in that it contains, in addition to the active substances 1 and 2 and the solvent, only benzalkonium chloride.

31) The Inhalable solution or suspension according to claim 20, characterised in that it is a concentrate or a sterile ready-to-use inhalable solution or suspension.

32) A method of nebulising in an inhaler according to WO 91/14468 or an inhaler as described in Figures 6a and 6b of WO 97/12687 comprising providing an inhalable solution according to claim 20.

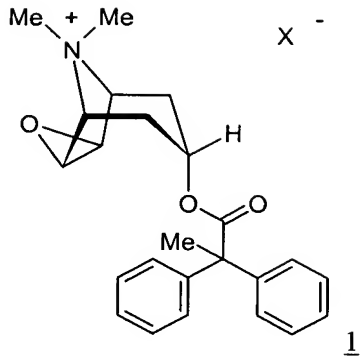
33) The method according to to claim 31 for nebulising in an energy-operated free-standing or portable nebuliser which produces inhalable aerosols by means of ultrasound or compressed air according to the Venturi principle or other principles.

34) The Propellant-containing inhalable aerosol according to claim 17, characterised in that the propellant gas is TG134a, TG227 or a mixture thereof.

35) A Method of treatment and/or prevention of a inflammatory or obstructive diseases of the respiratory tract comprising administering to a mammal in need of such a treatment a therapeutically effective amount of a composition according to claim 1.

36) A kit comprising:

(a) a first container containing a first pharmaceutical formulation comprising one or more anticholinergics of formula 1



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wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

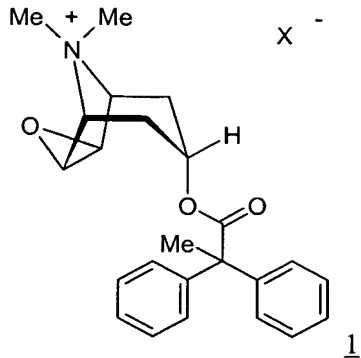
optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient

; and

(b) a second container containing a second pharmaceutical formulation comprising a one or more NK_1 receptor antagonists (2), optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates;

each container each optionally further containing a pharmaceutically acceptable excipient.

37) A Method of treatment and/or prevention of a inflammatory or obstructive diseases of the respiratory tract comprising administering to a mammal in need of such a treatment a therapeutically effective amount of the first pharmaceutical formulation (1) comprising one or more anticholinergics of formula 1



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wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

and second pharmaceutical formulation comprising one or more NK_1 receptor antagonists (2),

each of (1) and (2) optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient;

wherein the first and second pharmaceutical formulations are administered simultaneously or separately.